DM SHORT REPORT

Dobutamine Stress Echocardiography: False Positive Scans in Proteinuric Patients with Type 1 Diabetes Mellitus at High Risk of Ischaemic Heart Disease

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Patients with Type 1 diabetes mellitus have an increased risk of ischaemic heart disease (IHD). When diabetes is complicated by nephropathy this risk is further increased and asymptomatic IHD is common. New techniques for non-invasive cardiac evaluation are now available and one of these, Dobutamine Stress Echocardiography (DSE), was studied in subjects with Type 1 DM and nephropathy who had no evidence of IHD. DSE was performed on 18 subjects (13 male, 5 female; mean age 37.8 ± 3.4 years), diabetes duration 23.7 ± 1.2 years and nephropathy diagnosed for 10.9 ± 1.3 years. There were 7 (38 %) positive scans—suggesting asymptomatic IHD; 16.7 % of subjects studied had a significant arrhythmia. Coronary angiography was performed in 6 of the 7 subjects with positive DSEs and was positive in only 2. These results suggest that DSE has a high rate of false positive results in Type 1 DM patients suffering from nephropathy and may limit its usefulness in these subjects. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Patients with Type 1 diabetes mellitus have an increased risk of ischaemic heart disease (IHD),[1,2] especially when diabetes is complicated by nephropathy.[3–6] Asymptomatic IHD is common in diabetes mellitus and its presence is likely to have prognostic and therapeutic implications.[7] Advances in cardiology have introduced new non-invasive cardiac evaluations which can be used in the detection of asymptomatic IHD. These investigative tools include Exercise Thallium 201 Scintigraphy (ETS), Dipyridamole Thallium 201 Scintigraphy (DTS), and more recently Dobutamine Stress Echocardiography (DSE). The value of ETS and DTS have been discussed elsewhere[8–11] but little information is available on the value of DSE in diabetic subjects. It has been suggested that DSE is superior to both dipyridamole echocardiography and exercise electrocardiography for the diagnosis of coronary artery disease.[12] The sensitivity of DSE in non-diabetic patients with suspected IHD is 79–97 % with a specificity of 65–83 %[13–15] and it has been shown to be an accurate test with regard to the exclusion of significant coronary artery disease in a low risk population.[16] In one study of patients with Type 1 DM and end-stage renal failure (ESRF), DSE was incorporated into pre-transplant assessment and showed a high prevalence of abnormal tests and determined that positive testing was predictive of future cardiac events.[17]

The aim of this study was to evaluate the usefulness of DSE in the detection of asymptomatic IHD in a group of young, high-risk subjects with Type 1 DM and nephropathy, prior to ESRF, in whom there was no overt evidence of IHD.

Subjects and Methods

Inclusion Criteria

Subjects participating in the study were aged < 45 years, with duration of Type 1 DM > 15 years, and fixed proteinuria > 5 years. All subjects were required to have no clinical, or resting electrocardiographic, evidence of IHD and no clinical evidence of peripheral vascular disease. Standard cardiac risk factors were evaluated. Proteinuria was defined as 24 h urinary protein excretion

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of > 0.3 g. Hypertension was defined as a systolic blood pressure > 150 mmHg and/or a diastolic blood pressure > 95 mmHg recorded on 3 separate occasions. In a number of the individuals studied, blood pressure at the time of the study was controlled on combination antihypertensive therapy. Retinopathy was defined by ophthalmological assessment in the eye department which all our patients receive on a yearly basis. This was classified by a scoring system from 1 to 12 into none, background, and proliferative.

Patients were initially retrieved from a database which lists all subjects attending the clinic and their current complications. This list is updated annually. Following initial contact by letter, telephone contact was made and subjects invited to participate. Initial screening medical examination was performed with a subsequent appointment given for the procedure under evaluation. Thirty-six per cent of subjects responded positively to the request to participate in the study.

Dobutamine Stress Echocardiogram Protocol

Resting echocardiogram and electrocardiogram were recorded and dobutamine infused intravenously in a stepwise fashion. Subjects were started on 10 μg kg^{-1} min^{-1} for 4 min, then 20μg kg^{-1} min^{-1} for 3 min and finally 40 μg kg^{-1} min^{-1}, aiming for a heart rate of 90 % of the predicted, age-adjusted, maximal heart rate. If this was not achieved atropine was administered. The positive inotropic action of dobutamine increases myocardial oxygen demand and areas of ischaemia are detected by witnessing wall motion changes on echocardiography.[18] Twenty-two segments of myocardium were identified in accordance with American Society of Echocardiography guidelines and scored as being normal (1), hypokinetic (2), akinetic (3) or dyskinetic (4) with a resultant mean score. A wall motion abnormality was defined as a segment scoring 2 or greater in at least two different views. All DSEs were read by two blinded observers who were not aware of the diagnosis of diabetes mellitus or the aim of the study. Beta-blockers and calcium antagonists were discontinued for 48 h prior to the scans.

Subjects with positive DSEs had follow-up coronary angiography performed, ideally within 3 months of DSE. The study was approved by the local Ethics committee and subjects gave informed consent.

Results are presented as mean ± standard error for parametric data and as median ± semi-interquartile range for nonparametric data. Continuous data was compared using the unpaired Student's *t*-test for parametric variables and Mann-Whitney U for non-parametric variables. Discrete variables were compared using chi-squared analysis.

Results

Table 1 details the clinical characteristics of the group of 18 subjects (13M, 5F) who participated.

Dobutamine Stress Echocardiogram

All patients achieved the desired heart rate at 40 μg kg^{-1} min^{-1} and no subject required atropine. There were 7 positive scans among the 18 performed. There were no cases of negative scans associated with positive electrocardiographic changes or symptoms of angina. Those subjects with a positive scan were compared to those with negative scans and as Table 2 demonstrates that group with a positive scan had a trend towards longer duration of proteinuria, higher protein excretion, higher cholesterol and triglycerides, all non-significant.

During the infusions there were 3 (16.7 %) cases of significant arrhythmia: 1 case of symptomatic ventricular tachycardia (in a positive scan) and 2 cases of symptomatic supra-ventricular tachycardia (1 in a positive and 1 in a negative scan). The episode of ventricular tachycardia lasted for a salvo of 20 beats and the patient complained of retrosternal discomfort and palpitations. Dobutamine was immediately discontinued with prompt resolution of symptoms and electrocardiographic changes.

Coronary Angiography

Six of the patients with positive DSE scans proceeded to coronary angiogram within 3 months. The 7th developed unrelated neurological symptoms and signs and was excluded from further evaluation. Two subjects had positive angiograms—one male, one female. Both subjects had severe triple vessel disease which was inoper-

Table 1. Clinical characteristics of subjects

Number	18
M:F	13:5
Age (yr)	37.8 ± 3.4
Duration of Type 1 DM (yr)	23.7 ± 1.2
Duration of nephropathy (yr)	10.9 ± 1.3
24 h urinary protein (g 24 h^{-1})	0.5 ± 0.64
Creatinine (μmol l^{-1}, normal 60–130)	142.6 ± 24.6
HbA_{1C} (normal < 6.2 %)	8.3 ± 0.3
Cholesterol (mmol l^{-1})	5.7 ± 0.5
Triglycerides (mmol l^{-1})	1.1 ± 0.6
Current smokers	5
Family Hx atherosclerosis	3
Hypertension	13
Neuropathy on clinical exam	7
Retinopathy	
none	5
background	10
proliferative	3

Data given as means ± standard errors (as median ± semi-interquartile range for triglycerides and 24 h urinary protein).

Table 2. Comparison of patients with positive DSE to those with negative DSEs

	DSE +ve $n = 7$	DSE –ve $n = 11$	p value
M:F	6:1	7:4	0.596
Smoking	3 (43 %)	2 (18 %)	0.326
		R-R = 2.36	(0.52–10.75)
Hypertension	3 (43 %)	10 (91 %)	0.093
		R-R = 0.47	(0.2–1.13)
Fam Hx	0	3 (27 %)	0.245
Daily insulin dose (u kg^{-1})	0.54 ± 0.04	0.48 ± 0.4	0.607
Duration of proteinuria (yr)	11.3 ± 2.4	9.3 ± 1.4	0.254
Creatinine (μmol l^{-1}) (60–130)	171.5 ± 64.0	125.3 ± 12.8	0.382
24 h urinary protein[a] (g $24h^{-1}$)	0.23 ± 0.68	0.5 ± 2.13	0.421
Total cholesterol (mmol l^{-1})	6.4 ± 0.7	5.3 ± 0.3	0.051
Triglycerides (mmol l^{-1})[a]	1.6 ± 0.9	1.0 ± 0.44	0.071
HbA_{1C} (%) < 6.2 %	8.6 ± 0.4	8.2 ± 0.2	0.460

[a]Compared using Mann-Whitney U, remainder compared using unpaired *t*-test.

able in the male subject while the female subject was listed for coronary artery bypass surgery.

Discussion

This is the first reported study documenting the incidence of positive DSE in a population of diabetic subjects at risk of IHD who were entirely asymptomatic. A surprisingly high prevalence of positive scans was found in this young population. The 38 % positive scan rate in this study is identical to that reported previously in subjects with Type 1 DM and ESRF on a pre-transplant assessment programme.[17] We studied patients with no overt evidence of IHD, while 38 % of subjects in the previous study had an abnormal 12 lead ECG. That study detected only 1 false positive scan in the 18 subjects studied with both angiography and DSE while 4 of 6 in this study showed false positive scanning suggesting a positive predictive value for DSE in this cohort of 33 % (CI 4 %– 78 %).

The high prevalence of false positive DSE may be explained in a number of ways. Firstly these subjects with a long duration of DM and microvascular disease may be at risk of diabetic cardiomyopathy. This entity has been described previously[19] and could explain wall motion abnormality in the absence of coronary artery disease. Alternatively the presence of microvascular disease[20] may, theoretically, yield a positive DSE with angiography showing normal coronary circulation. Certainly the accuracy of exercise thallium 201 scintigraphy in the diabetic population has been questioned for this reason.[9] Finally these studies may represent true inducible ischaemia in subjects with intermediate grade coronary stenosis. Certainly DSE has been shown to prognosticate for the occurrence of cardiac events both in Type 1 DM[17] and in non-diabetic subjects.[15,21] These data are not yet available to us in this cohort but will be of interest in the future.

There were no significant differences between the two groups for standard cardiac risk factors though a trend was seen towards a longer duration of nephropathy, a higher 24 h protein excretion, and a higher level of cholesterol and triglycerides.

This study recorded a higher rate of occurrence of significant arrhythmias in a diabetic cohort than is suggested by the current literature which is derived from investigations performed on non-diabetic subjects.[15,22] Interestingly, the only reported case of non-ischaemic sustained ventricular tachycardia during DSE, that is ventricular tachycardia occurring in a patient with normal coronary arteries on angiography, was in a subject who had a history of Type 2 DM.[23] Autonomic denervation may render the diabetic patient more sensitive to circulating cathecholamines though this is only speculative as autonomic function tests were not available on the cohort studied here.

In conclusion, we found the value of Dobutamine Stress Echocardiography to be limited in this group of subjects with Type 1 DM and nephropathy due to a high incidence of false positive scans.

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